BC Cancer Protocol Summary for Palliative Combination Chemotherapy for Advanced Pancreatic Adenocarcinoma using Irinotecan, Oxaliplatin, Fluorouracil and Leucovorin

Protocol Code: *GIFIRINOX*

Tumour Group: *Gastrointestinal*

Contact Physician: *GI Systemic Therapy*

ELIGIBILITY:
- First line therapy for locally advanced or metastatic pancreatic adenocarcinoma.
- ECOG performance status less than or equal to 1
- Patients who have received single agent capecitabine or fluorouracil treatment first-line as the result of frailty, but who are now well enough to receive combination chemotherapy.
- Patients who have progressed on single agent capecitabine or fluorouracil therapy first-line and treatment escalation/combination chemotherapy is desired.
- Patients cannot receive both GIFIRINOX and GIPGEMABR sequentially. A BC Cancer Compassionate Access Program (CAP) approval is required prior to starting the second protocol if patients are intolerant to the first protocol ordered. Evidence of radiographic stable disease or response is required if 4 or more cycles of GIFIRINOX have been given. Switch of protocol due to intolerance is allowed only before cycle 9.

EXCLUSIONS:
- Ampullary Cancer
- CNS metastases
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Avoid in patients with congenital long QT syndrome.

CAUTIONS:
- Adequate marrow reserve, renal and liver function
- Patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness
- Patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy)
- Patients with symptomatic peripheral neuropathy
- Patients over 75 years of age
- Patients with baseline hyperbilirubinemia (greater than 26 micromol/L) not explained by degree of liver metastases

TESTS AND MONITORING:
- Baseline CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), sodium, potassium, magnesium, calcium, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine), appropriate imaging study and optional CEA, CA 19-9.
- **At the beginning of each cycle:** CBC and differential, platelets**,** creatinine, LFT's (bilirubin, ALT, alkaline phosphatase), sodium, potassium, magnesium, calcium
- If clinically indicated: CEA, CA 19-9
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR at beginning of each cycle.
- Baseline and routine ECG for patients at risk of developing QT prolongation (at the discretion of the ordering physician). See Precautions.
- Patients to be seen by physician at every cycle (every 2 weeks)
- Quantitative evaluation of disease response status every six to 10 weeks; discontinue therapy if any progression of disease.

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
- Atropine may be required for treatment or prophylaxis of diarrhea (see precautions)
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
- **Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration.**
- **Cryotherapy (ice chips) should NOT be used as may exacerbate Oxaliplatin-induced pharyngo-laryngeal dysesthesias.**

TREATMENT:

A cycle equals:

Drug	Dose	BC Cancer Administration Guidelines
oxaliplatin*	85 mg/m^2	IV in 250 to 500 mL of D5W over 2 hours immediately followed by
leucovorin	400 mg/m^2	IV in 250 mL D5W over 1 hour 30 minutes
irinotecan	180 mg/m^2	IV in 500 mL of D5W over 1 hour 30 minutes** Immediately followed by
fluorouracil	400 mg/m^2	IV push, followed by
fluorouracil	2400 mg/m^2	IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 INFUSOR ***

Repeat every 14 days until disease progression.

**** Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.***

***** Irinotecan and leucovorin may be infused at the same time by using a Y-connector placed immediately before the injection site. Irinotecan and leucovorin should not be combined in the same infusion bag. Leucovorin dose remains at 400 mg/m^2 IV over 1 hour and 30 minutes when concurrent irinotecan is omitted.***

*** *A*lternative administration:

- For 3000 to 5500 mg dose **select INFUSOR per dose range below (doses outside** dose banding range are **prepared as ordered**)**:**

Dose Banding Range	Dose Band INFUSOR (mg)
Less than 3000 mg	Pharmacy to mix specific dose
3000 to 3400 mg	3200 mg
3401 to 3800 mg	3600 mg
3801 to 4200 mg	4000 mg
4201 to 4600 mg	4400 mg
4601 to 5000 mg	4800 mg
5001 to 5500 mg	5250 mg
Greater than 5500 mg	Pharmacy to mix specific dose

- Inpatients: 1200 mg/m^2/day in 1000 mL D5W by continuous infusion daily over 23 h for 2 days

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

All patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with directions for the management of diarrhea.

DOSAGE MODIFICATIONS (A, B & C):

Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

A. Dose Modifications for NEUROLOGIC Toxicity
B. Dose Modifications for HEMATOLOGIC Toxicity
C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

Table 1 - Dose Reduction Levels for All Toxicity

Agent	Starting Dose	Dose Level -1	Dose Level -2*
irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
fluorouracil IV push	400 mg/m^2	320 mg/m^2	200 mg/m^2
fluorouracil Infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2

If IV push fluorouracil is delayed/omitted**, **folinic acid (leucovorin) should also be delayed/omitted.

**** For any additional dose reductions, use 20% less than previous level or consider discontinuing this regimen.***

Table 2 - Oxaliplatin Neurotoxicity Definitions

Grade 1	Paresthesias / dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re-challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed

A. Dose Modifications for Oxaliplatin NEUROLOGIC Toxicity

Toxicity Grade	**Duration of Toxicity**		**Persistent (present at start of next cycle)**
	1 – 7 days	**greater than 7 days**	
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Decrease 1 dose level
Grade 3	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	Discontinue
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngolaryngeal **(see precautions)**	Increase duration of infusion to 6 hours	N/A	N/A

B. Dose Modifications for HEMATOLOGIC Toxicity based on day 1 CBC

NOTE: Dose reductions should be maintained for subsequent cycles.

<table>
<tr><th></th><th>CYCLE DELAY</th><th colspan="3">DOSE REDUCTION</th></tr>
<tr><th></th><th></th><th>irinotecan</th><th>oxaliplatin</th><th>leucovorin/fluorouracil</th></tr>
<tr><td>ANC greater than or equal to 1.5 x 10^9/L and Platelets greater than or equal to 75 x 10^9/L</td><td>No cycle delay</td><td colspan="3">No dose reduction</td></tr>
<tr><td rowspan="2">ANC greater than or equal to 1 x 10^9/L and less than 1.5 x 10^9/L</td><td rowspan="2">Delay the treatment until ANC greater than or equal to 1.5 x 10^9/L

If no recovery in 2 weeks, discontinue the treatment*.</td><td>1st episode: dose reduction to 150 mg/m^2

2nd episode: maintain dose at 150 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: no dose reduction

2nd episode: dose reduction to 65 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: reduce the IV push fluorouracil and the infusional fluorouracil by one dose level

2nd episode – eliminate the IV push fluorouracil and leucovorin infusion and maintatin infusional fluorouracil at dose level -1

3rd episode: discontinue the treatment</td></tr>
<tr><td colspan="3">NOTE: Dose reductions should be maintained for subsequent cycles.</td></tr>
<tr><td rowspan="2">ANC greater than or equal to 0.5 10^9/L and less than 1.0x 10^9/L</td><td rowspan="2">Delay the treatment until ANC greater than or equal to 1.5 x 10^9/L

GCSF support should be considered

If no recovery in 2 weeks, discontinue the treatment.</td><td>1st episode: dose reduction to 150 mg/m^2

2nd episode: dose reduction to 120 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: no dose reduction

2nd episode: dose reduction to 65 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: eliminate the IV push fluorouracil and leucovorin infusion and reduce the infusional fluorouracil by one dose level

2nd episode: maintain the reduced dose

3rd episode: discontinue the treatment</td></tr>
<tr><td colspan="3">NOTE: Dose reductions should be maintained for subsequent cycles.</td></tr>
</table>

	CYCLE DELAY	DOSE REDUCTION		
		irinotecan	**oxaliplatin**	**leucovorin/fluorouracil**
ANC less than 0.5 x 10^9/L	Delay the treatment until ANC greater than or equal to 1.5 x 10^9/L **GCSF support should be considered** If no recovery in 2 weeks, **discontinue the treatment**.	**1st episode**: dose reduction to 150 mg/m^2 **2nd episode**: dose reduction dose at 120 mg/m^2 **3rd episode**: **discontinue the treatment**	**1st episode**: dose reduction to 65mg/m2 **2nd episode**: dose reduction to 50 mg/m^2 **3rd episode**: **discontinue the treatment**	**1st episode**: eliminate the IV push fluorouracil and leucovorin infusion and reduce the infusional fluorouracil by one dose level **2nd episode**: maintain the reduced dose **3rd episode: discontinue the treatment**
		NOTE: Dose reductions should be maintained for subsequent cycles.		
Platelets greater than or equal to 50 x 10^9/L and less than 75 x 10^9 /L	Delay the treatment until recovery (platelets greater than or equal to 75x10^9/L). If no recovery in 2 weeks, **discontinue the treatment**.	**1st episode**: no dose reduction **2nd episode**: reduce the dose to 150 mg/m^2 **3rd episode**: **discontinue the treatment**	**1st episode**: dose reduction to 65 mg/m² **2nd episode**: maintain the reduced dose **3rd episode**: **discontinue the treatment**	**1st episode**: reduce the IV push fluorouracil and the infusional fluorouracil by one dose level **2nd episode**: maintain the reduced dose **3rd episode: discontinue the treatment**
		NOTE: Dose reductions should be maintained for subsequent cycles.		
Platelets less than 50 x10^9 /L	Delay the treatment until recovery (platelets greater than or equal to 75x10^9/L). If no recovery in 2 weeks, **discontinue the treatment**.	**1st episode**: no dose reduction **2nd episode**: dose reduction to 150 mg/m^2 **3rd episode**: **discontinue the treatment**	**1st episode**: dose reduction to 65 mg/m² **2nd episode**: dose reduction to 50mg/m2 **3rd episode**: **discontinue the treatment**	**1st episode**: reduce the IV push fluorouracil and the infusional fluorouracil by one dose level **2nd episode** – eliminate the IV push fluorouracil and leucovorin infusion and maintain the infusional fluorouracil at dose level -1 **3rd episode**: **discontinue the treatment**
		NOTE: Dose reductions should be maintained for subsequent cycles.		

C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

At the Beginning of a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	**Diarrhea**	
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Increase of 2 to 3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level
	2	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level
	3	Increase of 7 to 9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 1 dose level of irinotecan and infusional fluorouracil. Discontinue IV push fluorouracil and leucovorin.
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level of oxaliplatin and infusional fluorouracil. Discontinue irinotecan, IV push fluorouracil and leucovorin.
	Grade	**Stomatitis**	
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Painless ulcers, erythema or mild soreness	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	↓ 1 dose level of IV push and infusional fluorouracil
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 1 dose level of oxaliplatin, irinotecan and infusional fluorouracil. Discontinue IV push fluorouracil and leucovorin.

PRECAUTIONS:

1. **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required. (see below)
   For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity premedication:
   45 minutes prior to oxaliplatin:
   - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

   30 minutes prior to oxaliplatin:
   - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

   Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications.
   The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication. Various desensitization protocols using different dilutions and premedications have been reported. Refer to SCOXRX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.
2. **Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table).

Clinical Symptoms	**Pharyngo-laryngeal Dysesthesia**	**Platinum Hypersensitivity**
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

3. **Pulmonary toxicity:** Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely with oxaliplatin. Supportive care is required. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed **oxaliplatin should be discontinued.**

4. **Diarrhea:** may be life threatening and requires prompt, aggressive treatment.
   - **Early diarrhea** or abdominal cramps occurring within the first 24 hours is treated with **atropine** 0.3 to 1.2 mg IV or SC. Prophylactic atropine may be required for subsequent treatments.
   - **Late diarrhea** has an onset of 5 to 11 days post-treatment, a duration of 3 to 7 days and must be treated promptly with **loperamide** (eg, IMODIUM®). The loperamide dose is higher than recommended by the manufacturer. Instruct patient to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent stool than usual:
     - **4 mg stat**
     - **then 2 mg every 2 hours until diarrhea-free for 12 hours**
     - may take 4 mg every 4 hours at night
   - The use of drinks such as GATORADE® or POWERADE® to replace fluid & body salts is recommended.
   - Consideration should be given to the use of an oral fluoroquinolone (e.g., ciprofloxacin) in patients with persistent diarrhea despite adequate loperamide or if a fever develops in the setting of diarrhea, even without neutropenia. If diarrhea persists for longer than 48 hours then hospitalization for parenteral hydration should be considered.
5. **Other cholinergic symptoms:** may occur during or shortly after infusion of irinotecan including rhinorrhea, increased salivation, lacrimation, diaphoresis and flushing. These should be treated with atropine 0.3 mg to 0.6 mg IV or SC. This dose may be repeated at the physician's discretion. Blood pressure and heart rate should be monitored. Prophylactic atropine may be required for subsequent treatments.
6. **QT prolongation and torsades de pointes** are reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg po would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.
7. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. **GCSF support should be initiated for further cycles after an episode of febrile neutropenia.**
8. **Gilbert's syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.
9. **Hepatic dysfunction:** Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or ALT greater than 3x the upper limit of normal if no liver metastases, or ALT greater than 5x the upper limit of normal with liver metastases. The risk of severe neutropenia may be increased in patients with a serum bilirubin of 17 to 35 micromol/L.
10. **Prior pelvic radiotherapy** or radiotherapy to greater than 15% of the bone marrow bearing area may increase the degree of myelosuppression associated with this regimen, and caution is recommended in these cases. Close monitoring of the CBC is essential.
11. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
12. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.

13. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
14. **Venous Occlusive Disease** is a rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
15. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.
16. **Potential Drug Interactions:** Anticonvulsants and other drugs which induce Cytochrome P450 3A4 isoenzyme activity e.g. carbamazepine, phenytoin and St John's Wort may decrease the therapeutic and toxic effects of irinotecan. Prochlorperazine may increase the incidence of akathisia and should be avoided on the day of irinotecan treatment.
17. **Possible drug interaction with fluorouracil and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during fluorouracil therapy is recommended until a stable warfarin dose is established. Thereafter, INR prior to each cycle. Consultation to cardiology/internal medicine should be considered if difficulty in establishing a stable warfarin dose is encountered. Upon discontinuation of fluorouracil, repeat INR weekly for one month.
18. **Possible drug interaction with fluorouracil and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Fluorouracil may increase the serum concentration of these two agents.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

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6. Mathijssen RHJ, Verweij J, de Bruijn P, et al. Effects of St. John's Wort on irinotecan metabolism. J Natl Cancer Inst 2002;94(16):1247-9.